Research Activities from the Laboratory of Karen Hendricks-Munoz, MD, MPH

Karen Hendricks-Munoz MD, MPH arrived in February, 2012 to become Chief of the Division of Neonatal Medicine and the first occupant of the William Tate Graham Chair in Neonatology. Karen graduated from both Yale Medical School and Yale School of Public Health, and stayed on there for her pediatric residency. She did her neonatal fellowship at the University of Rochester, where she then worked as an assistant professor for six years. After a brief sojourn in Miami, she became the Division Chief of Neonatology at New York University in 1990 and rose to become Professor and Associate Chair of Pediatrics.

Karen can trace her research interests to her medical school days. “I actually fell in love with cell biology as a medical student at Yale when I heard a lecture from George Emil Palade, (Nobel Laureate) who discovered the golgi apparatus!! Dr. Palade was the Chair of Cell Biology at Yale and I was privileged to hear him often and, well, I have been hooked ever since!!”

Her early federally funded work was in the cellular mechanism of surfactant production, focused on regulation of surfactant trafficking in the type 2 cell especially the response to environmental changes such as steroids or hyperoxia. These results led to further interest in endothelial pulmonary cell interaction and endothelial cell regulated vascular growth and dysfunction so she moved into how endothelial cells impact all cells because of the dependency for oxygen, toxic clearances etc. She focused on a model of vascular growth related to preterm blindness/retinopathy and fetal loss. Through her work, the roles of drugs of abuse, caffeine, sepsis on retinal health and perturbed vascular development were discovered.

Her lab identified the indirect environmental effects sepsis can have, particularly the impact of bacteria/ fungus on endothelial cell and vascular development. This was coupled to observations on the beneficial effects on not just the baby but cellular mechanisms of skin-skin contact between mothers and their babies, which led to my most recent NIH grant on the transmission of maternal indigenous bacteria to the newborn through Kangaroo Maternal Care. It is one aspect of the overall goal to understand the crosstalk of the microbiome repertoire in developing infant health.

According to Karen, we are just beginning to appreciate the role of the microbiome … (Continued on Page 2)
- the collection of microbes living on and inside us – in triggering disease, as well as in promoting wellness. The core microbiome is established over the first year of life and its composition is thought to be affected by external factors, including birth route (vaginal vs. caesarian), diet (breast milk vs. formula, introduction of solid foods), and antibiotic use. Several studies have demonstrated that differences in the diversity or composition of the gut microbiota can be associated with disease states, including diseases believed to have an environmental component, such as obesity and autism. The fact that the microbiome is so readily affected by external and maternal factors (we have identified that maternal steroids and antibiotics change the initial oral microbiome composition in the mother and the infant) suggests that it may also be influenced by a number of other environmental insults, including exposure to environmental chemicals. This is particularly intriguing because the microbiome is thought to be established during the first few years of life, a time also known to be highly sensitive to the effects of exposure (i.e. the Developmental Origins of Health and Disease, Barker theory). Gaining a better understanding of the complex relationship between microbiota, microbial metabolism and viruses and the integrated environment may explain why some individuals are more susceptible to environmental exposures than others, or have worse health trajectories. This potentially could completely revolutionize the way we currently think about these microbes contribution to human disease.

What brought her to VCU and CHOR at VCU? “VCU was attractive because of the work currently be performed here in the microbiome. Very few centers have a focused approach to understanding the role of our commensal “friends” in our health development. The colleagues here are also eager to collaborate and think outside the box which was exciting. This exploratory and open view permeates the place from the President, the Dean, our Chair, to the nurses in the NICU! The center for biological complexity directed by Greg Buck offers incredible support for the work we are doing,” she says.

This is reflected by the multiple projects with which Karen is involved. Along with continuing her NIH work on the impact of maternal infant interaction and kangaroo care on the microbiome, with Gregory Buck, PhD and Nihar Seth, MS of the VCU Center for Biological Complexity, she has projects on:

- **Microbial and metabolomics development of the preterm infant** – do specific microbial cytokine associated repertoires increase risk or can be biomarkers for intestinal health and disease - with Greg Buck, Jenny Fox MD and Jie Xu, Ph.D. from Neonatal Medicine, Leroy Thacker, PhD from Biostatistics and Ping Xu PhD of the VCU Philips Institute, School of Dentistry.
- **Fetal and infant microbial changes associated with maternal environmental exposures to diesel pollutants** - Greg Buck, Nihar Seth, Jie Xu, Judith Voynow MD (CHOR at VCU’s Division of Pediatric Pulmonology) and Rick Auten, MD, Duke University Department of Pediatrics.
- **Microbial cytokine patterns as predictors of pulmonary health in the NICU** - Joseph El-Khoury, MD from Neonatal Medicine along with Greg Buck and Nihar Sheth.
- **Early microbial development and risk for later obesity/diabetes** - Romesh Wijesooriya, MD of the Division of General Pediatrics and Shumei Sun, PhD from the Department of Biostatistics.
- **Impact of the microbiome during pregnancy and preterm birth risk** - Greg Buck Philippe Girerd, MD from the Department of OB/GYN, Nihar Sheth, Jie Xu and others.
- **Microbial interactions in gastrin releasing peptide and bronchopulmonary dysplasia** - with Judy Voynow and others.

As if these aren’t enough, Karen is already thinking about the next phase. When asked where she sees this going, she said, “New information has uncovered a strong relationship between the gut microbiome and the brain which is believed to be bi-directional, i.e., signals from the gut microbiota may modulate brain function and the brain may alter the gut microbiome, e.g., by changing gastrointestinal motility and intestinal permeability. I am interested in communication from the microbiota in the gut to the brain especially identifying specific pathways and mechanisms involved in the communication between the gut microbiome and the brain endothelial interface.”

What Karen Hendricks-Munoz has done since her arrival less than 18 months ago illustrates how modern research works best; putting the right people in the right environment, and creating collaborations that cut across traditional lines.

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The Research of Dr. Karen Hendricks-Munoz Continued ….
The Role of RAGE and ADAM-10 in Pediatric Metabolic Syndrome

The cell membrane bound receptor of Advanced Glycation Endproducts (mRAGE) is induced by ligands [such as advanced glycation end products (AGEs) which are present in common western diet] to activate intracellular pro-oxidant and pro-inflammatory signals. Additionally, the circulating form of RAGE (sRAGE) is proposed to act as a decoy receptor to clear AGEs. Studies in adults with cardiovascular disease, diabetes and MetS show inverse correlation of disease state with sRAGE and direct correlation with mRAGE. The AGEs and RAGE may play an important role in the oxidative stress and inflammation that leads to insulin resistance (IR), features of Metabolic Syndrome (MetS) in children. However, studies of AGEs and RAGE variants in children are very few. W hypothesize that 1) AGE-RAGE alterations are present early in MetS, 2) decrease in IR after a lifestyle intervention reflects increase in sRAGE or decrease in mRAGE, 3) the enzyme ADAM-10 destabilizes cell surface RAGE to increase sRAGE and decrease mRAGE 4) ADAM-10 sheds mRAGE to generate protective sRAGE. W will determine AGEs, sRAGE levels, mRAGE and ADAM-10 in peripheral blood mononuclear cells as well as dietary AGE intake and IR indices in 60 obese adolescents at baseline, 3 months and 6 months of intensive lifestyle intervention. In the laboratory, we will generate a liver specific ADAM-10 Knock out (ADAM-10 HKO) model. With this model, we will assess the effect of ADAM-10 on mice fed a western style high-AGE diet, assessing glucose/insulin tolerance, aminotransferases, lipids, AGEs and sRAGE, inflammatory...
Congratulations to the following Principal Investigators who were awarded grants and contracts in the First Half of 2013!

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Division</th>
<th>Title</th>
<th>Sponsor</th>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bean, Melanie</td>
<td>Endocrinology</td>
<td>Motivational interviewing in NOURISH for parents of overweight children</td>
<td>American Heart Association</td>
<td>77,000</td>
</tr>
<tr>
<td>Kumar, Santosh</td>
<td>Allergy/Immunology</td>
<td>Multicenter-open label controlled Phase III study to assess the efficacy, tolerability, safety and pharmacokinetics of Kedrion IVIG 10% in adult and pediatric patients with primary immunodeciency</td>
<td>Atlantic Research Group</td>
<td>81,758</td>
</tr>
<tr>
<td>Godder, Kamar</td>
<td>Heme-Onc</td>
<td>Master subaward agreement for industry funding sources—CHOP/VCU/COG</td>
<td>Children’s Hospital of Philadelphia</td>
<td>0</td>
</tr>
<tr>
<td>Meloy, Linda</td>
<td>General Peds</td>
<td>MMR-160 GSK Biologicals’ MMR vaccine (203762) compared to Merck 7 Co Inc’s MMR vaccine as a first dose both co-administered with Varivax, Havrix and Prevnar13 (subset of children) to healthy children 12 to 15 months of age</td>
<td>GlaxoSmithKline</td>
<td>120,560</td>
</tr>
<tr>
<td>Williams, Ron</td>
<td>Pulmonology</td>
<td>A Phase II randomized double-blind placebo-controlled repeat dose study of KB001-A in subjects with cystic fibrosis infected with pseudomonas aeruginosa</td>
<td>KaloBios Pharmaceuticals</td>
<td>167,350</td>
</tr>
<tr>
<td>Williams, Ron</td>
<td>Pulmonology</td>
<td>A Phase II randomized double-blind placebo-controlled repeat dose study of KB001-A in subjects with cystic fibrosis infected with pseudomonas aeruginosa</td>
<td>KaloBios Pharmaceuticals</td>
<td>9,875</td>
</tr>
<tr>
<td>Schmidt, H Joel</td>
<td>Pulmonology</td>
<td>A Phase 3 two-arm rollover study of long term ivacator treatment in subjects 6 years of age and older with cystic fibrosis and a non-G551D CFTR mutation</td>
<td>Vertex Pharmaceuticals</td>
<td>67,398</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>$523,391</strong></td>
</tr>
</tbody>
</table>

For the 2012-13 academic year, there were 40 funded grants, contracts and extensions awarded to 19 faculty members from 9 divisions.

In money terms according to InfoEd, direct costs were $4,270,023, F & A costs $815,533 and totals were $5,085,346. This is a 1.5% drop in direct costs compared to the last academic year. However, prospects for 2013-14 are looking very good!

Anyone with a grant application, or an inquiry or an idea is encouraged to call the Pediatric Research Office. We can help with regulatory document review and preparation (OSP, IRB, WIRB, IACUC), with budget preparation, with getting signatures or with finding resources within the University to help you accomplish your research goals. Call or email Sharon Dawson, Jaime Petrasek or Henry Rozycki.


Morhardt DR, Barrow W, Jaworski M, Accardo PJ. Head Circumference in Young Children With Autism: The Impact of Different Head Circumference Charts. J Child Neurol. 2013 Jan 17. [Epub ahead of print]


Schecter MS. Wealth as a disease modifier in cystic fibrosis. The Lancet Respiratory Medicine 2013; 1: 93-95


Irwin RS, Augustyn N, French CT, Rice J, Tedeschi V, Welch SJ; Editorial Leadership Team. Spread the word about the journal in 2013: from citation manipulation to invalidation of patient-reported outcomes measures to renaming the Clara cell to new journal features. Chest. 2013 Jan;143(1):1-4. (BK Rubin)


Mason MJ, Keyser-Marcus L, Snipes D, Benotsch E, Sood B. Perceived Mental Health Treatment Need and Substance Use Correlates Among Young Adults. Psychiatr Serv. 2013 May 15. [Epub ahead of print]


The Children’s Hospital of Richmond at VCU has its first listing in the US News and World Report of the 2013-14 Best Children’s Hospitals. Congratulations to Drs. Timothy Bunchman John Hurley and Megan Lo and Lauren Barnhart on their achievement!

Dr. Bruce Rubin, Jesse Ball Dupont Distinguished Professor and Chairman of Pediatrics was guest speaker at the following:

  - Myths, mistakes, and dogma in CF. [2] Bordatella infection in cystic fibrosis. Also was judge of the poster competition

Dr. Michael Schechter, Chair of Pediatric Pulmonology was at the European Cystic Fibrosis Conference in Lisbon, Portugal in June 2013 where he:

  - Chaired a symposium on Outcome Determinants of CF. [2] Gave a presentation on The Socio-economic Outcome Determinants in CF.

Dr. Tim Bunchman, Chair of Pediatric Nephrology attended and presented at the following:

- 40th Year of the University of Miami Pediatric Nephrology course, March 14-16, 2013, Miami, Fl “AKI in the PICU: Managing RRT”
- Urology and Nephrology Foundation of America Kidney in Crisis: Acute Care Pediatric Nephrology Sponsored by Einstein University School of Medicine, Mar 22, 2013, New York, NY “Use of CRRT in Pediatrics: Pearls for the Clinician”
- NIH review board for the CKIDs (Chronic Kidney Disease in Children) , Bethesda MD, April 2013
- NIH section chief in cooperation with the NIDDK on Workshop on AKI in the Neonatal population, Bethesda, MD, April 2013

PAPERS PRESENTED AT THE PEDIATRIC ACADEMIC SOCIETIES ANNUAL MEETING  
WASHINGTON DC, MAY 4-7 2013

Simon Karam, Karen D. Hendricks-Munoz, Jie Xu, Henry Rozycki. Multiplex Cytokine Analysis from Tracheal Aspirates in ELBW Infants: Relationship to Ventilation and Interactions.

Tazuddin A. Mohammed, Russell R. Moores, Jr., Henry J. Rozycki, Kevin R. Ward. Microvascular Oxygen Saturation by Non-Invasive Raman Spectroscopy Correlates With Central Venous Oxygen Saturation in Newborn Infants

Mamatha Kambalapalli, Gary L. Francis, Xiaoyong Lei, Sasanka Ramanadham, Suzanne E. Barbour. iPLA2β Regulates Pre-mRNA Splicing of Apoptosis Regulators in Pancreatic β-Cells

Linda Dianne Meloy and Donna Halloran. Session Moderator- General Pediatrics: Newborn Care.

Tazuddin A. Mohammed, Jose L. Munoz, Russell R. Moores, Jr., Jie Xu, Sharon A. Cone, Janis Faye Ober, Susan Collins Lewis, Michael B. Edmond, Karen D. Hendricks-Munoz. Methicillin Resistant Staphylococcus Aureus (MRSA) and the Individual Room Neonatal Intensive Care Unit

Truc Hoang, Pradeep V. Mally, Jie Xu, Karen D. Hendricks-Munoz. Salivary Cytokine Analysis in Preterm Infants: Relationship to Early Delivery and Levels in the Well Full Term Infant

Christine M. Pennesi, Benjamin R. Greene, Truc Hoang, Yang Kim, Karen D. Hendricks-Munoz. Impact of Utilization of Kangaroo Mother Care on Preterm Infant Outcomes in the Neonatal Intensive Care Unit

Sean M. Bailey, Karen D. Hendricks-Munoz, Pradeep Mally. Cerebro-Splanchnic Oxygen Ratio (CSOR) Values in Healthy Term Infants as Measured by Near-Infrared Spectroscopy (NIRS)

Shadi R. Jurdi, Archana Jayaram, Tazuddin A. Mohammed, Jenny Fox, Russell Moores, Joe El Khoury, Gail Baker, Sharon Cone, Karen Hendricks-Munoz. Sustained Quality Improvement Initiatives Improve Neonatal Morbidities in Premature Infants – A Unit’s Experience

PAPERS PRESENTED AT THE AMERICAN THORACIC INTERNATIONAL MEETING  
PHILADELPHIA PA, MAY 18-22, 2013

E. Tokita, MD, Ph.D., T. Tanabe, M.D. Ph.D., K. Asano, Ph.D., H. Suzaki, MD.Ph.D., B.K. Rubin, MEng, MD, MBA. Clara (Club) Cell 10-kDa Protein Attenuates Endotoxin Induced Inflammation In Differentiated Human Bronchial Epithelial Cells,

T. Tanabe, MD, PhD, S.R. Webb-Parker, N/A, E. Tokita, MD, Ph.D., B.K. Rubin. Inflammasome Profiling By Multiplex Analysis In Airway Goblet Cell Culture
PAPERS PRESENTED AT THE ENDO 2013, SAN FRANCISCO, CA JUNE 15-18

Mamatha Kambalapalli. Regulation of RAGE Splicing by iPLA2β

PAPERS PRESENTED AT THE SOCIETY FOR HOSPITAL MEDICINE ANNUAL MEETING, NATIONAL HARBOR, MD MAY 16-19

1) Farah Siam, MD, Jessica Addison, MD, Clifton Lee MD. Recurrence of Kawasaki Disease

2) Gary Beasley, MD, Clifton Lee, MD. Infectious Endocarditis in Children: One Institution's Analysis

3) Stefanie Reed, DO, Clifton Lee, MD. When Eczema Changes: Case Report and Literature Review

PAPERS PRESENTED AT THE AMERICAN TRANSPLANT CONFERENCE, SEATTLE, WA MAY 18-22


Behnke M, Fisher RA, Reimers M. Exploring the role of embryonic liver development genes in HCV induced cirrhosis and hepatocellular carcinoma.


Behnke M, Reimers M, Fisher RA. Hepatocyte proliferation is inhibited in Hepatitis C-induced cirrhosis and loss of this inhibition defines a sub-type of Hepatitis C-induced hepatocellular carcinoma with poor prognosis. 4th International Conference on Transplantomics and Biomarkers in Organ Transplantation, Cambridge UK March 2013.


Anyone with an award, including editorial boards, study sections, medals, lectureships etc., or who have given lectures or research presentations at meetings outside of VCU, please send the information to Henry Rozycki at hrozycki@mcvh-vcu.edu for inclusion in the next newsletter.
What is OnCore?

OnCore is a Clinical Trial Management System (CTMS) developed by Forte Research that is the most widely adopted among academic research universities nationwide. OnCore is a web-based CTMS providing users secure access from any location to record, manage and report on data associated with the operation of clinical trials.

How will VCU use OnCore?

Massey Cancer Center has been using OnCore successfully since 2006. In November, 2012, VCU initiated the OnCore enterprise-wide expansion to schools and departments outside of Massey Cancer Center who conduct clinical trials. OnCore will serve as the system of record for VCU clinical trials data. Current methods of recording and tracking protocol activity will be replaced by OnCore. OnCore will strengthen research infrastructure, optimize study management processes and workflows to enable study teams to more effectively and efficiently manage clinical trials both from operational and administrative standpoints.

What will OnCore do for me?

- **Protocol & Subject Life Cycle Management**: Set-up and track protocols, monitor accrual, report on study activity.
- **Subject Safety Management**: Automated notifications for AE, SAE tracking, outside safety report tracking, IRB reporting.
- **Protocol & Subject Calendar Management**: Calendars maintain study parameters including treatment administration, evaluations, and data collection schedules. Subject-specific calendars are automatically generated for subject visit tracking which drives the financial management functionality.
- **Study Financial Management**: Life cycle financial management from documentation of coverage analysis, to budget negotiation, to tracking milestone payments, invoice creation, and payment reconciliation.
- **Study Information Portal**: Provides up-to-date protocol information for community consumption.

What are the benefits of OnCore to a PI?

- **Secure, web-based system**: Data, consent forms, study calendars, etc. can be accessed from any computer.
- **Easily answer questions**, such as: How many protocols are open to accrual? How many subjects are on treatment? What is my enrollment limit?
- **Strengthened compliance**: Tracking regulatory approvals, staff training, coverage analysis, adverse event documentation.
- **Increased efficiency between PI, Coordinator, and financial staff** to ensure compliant billing and sound financial management.

Want more details?

Contact us to learn more about OnCore, the implementation schedule and upcoming demo/training sessions.

Marjorie Halverson, RN, OCN, CCRP
SoM Implementation Coordinator | mhalverson@vcu.edu | 828.1902

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OnCore Implementation Project Officer | jdeshazo@vcu.edu | 828.5509

Learn more at go.vcu.edu/oncore